AHFS Category 80:12

271-371
3107700-3107710-3107736

Influenza Virus Vaccine
Fluzone®
2006 – 2007 Formula

Flu

℞ only

DESCRIPTION

Fluzone®, Influenza Virus Vaccine, (Zonal Purified, Subvirion) for intramuscular use, is a sterile suspension prepared from influenza viruses propagated in embryonated chicken eggs. The virus-containing fluids are harvested and inactivated with formaldehyde. Influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted using a nonionic surfactant, octoxinol-9, (Triton® X-100 – A registered trademark of Union Carbide, Co.) producing a "split virus." The split virus is then further purified by chemical means and suspended in sodium phosphate-buffered isotonic sodium chloride solution. Fluzone vaccine has been standardized according to USPHS requirements for the 2006–2007 influenza season and is formulated to contain 45 micrograms (µg) hemagglutinin (HA) per 0.5 mL dose, in the recommended ratio of 15 µg HA each, representative of the following three prototype strains: A/New Caledonia/20/99 (H1N1), A/Wisconsin/67/2005 (H3N2) and B/Malaysia/2506/2004.[1] Gelatin 0.05% is added as a stabilizer. Fluzone vaccine is supplied in four different presentations: a 5 mL vial of vaccine which contains the preservative thimerosal [(mercury derivative), (25 µg mercury/dose)]; a 0.25 mL prefilled syringe (No Preservative: Pediatric Dose, for 6–35 months of age) distinguished by a pink syringe plunger rod; a 0.5 mL prefilled syringe (No Preservative, for 36 months of age and older); and a single dose vial (No Preservative, for 36 months of age and older). There is no thimerosal used in the manufacturing process of the No Preservative unit dose presentations of Fluzone vaccine. Fluzone vaccine, after shaking syringe/vial well, is essentially clear and slightly opalescent in color.

ANTIBIOTICS ARE NOT USED IN THE MANUFACTURE OF FLUZONE VACCINE.

ALL PRESENTATIONS OF FLUZONE VACCINE ARE LATEX-FREE.

CLINICAL PHARMACOLOGY

Influenza is a significant cause of death and, along with pneumonia, is the seventh leading cause of death across generations.[2] This understates the actual impact of influenza as the complications associated with influenza infection are also categorized as heart disease, chronic lower respiratory disease, or diabetes.[3] As a result, influenza each year conservatively contributes to over 36,000 deaths,[1] many of which could be prevented through vaccination. Influenza viruses also can cause pandemics during which rates of illness and death from influenza-related complications can increase dramatically. Influenza viruses cause disease among all age groups. Rates of infection are highest among children, but rates of serious illness and death are highest among persons aged ≥65 years and persons of any age who have medical conditions that place them at increased risk for complications from influenza.[1]

Influenza vaccination is the primary method for preventing influenza and its severe complications. The primary target groups recommended for annual vaccination are 1) groups that are at increased risk for influenza-related complications (eg, persons aged ≥65 years, children aged 6–23 months, pregnant women, and persons of any age with certain chronic medical conditions); 2) persons aged 50–64 years because this group has an elevated prevalence of certain chronic medical conditions; and 3) persons who live with or care for persons at high risk (eg, health-care workers and household contacts who have frequent contact with persons at high risk and who can transmit influenza to persons at high risk). Vaccination is associated with reductions in influenza-related respiratory illness and physician visits among all age groups, hospitalization and death among persons at high risk, otitis media among children, and work absenteeism among adults.[1]

Among persons aged ≥65 years, influenza vaccination levels increased from 33% in 1989 to 66% in 1999, surpassing the Healthy People 2000 goal of 60%. Although estimated influenza vaccination coverage for the 1999–2000 season reached the highest levels recorded among older black, Hispanic, and white populations, vaccination levels among blacks and Hispanics continue to lag behind those among whites.[1]

Increasing vaccination coverage among persons who have high-risk conditions and are aged <65 years, including children at high risk, is the highest priority for expanding influenza vaccine use.[1]

Vaccination of health-care workers has been associated with reduced work absenteeism and fewer deaths among nursing home patients. Efforts should be made to educate health-care workers regarding the benefits of vaccination and the potential health consequences of influenza illness for themselves and their patients.[1]

Influenza A and B are the two types of influenza viruses that cause epidemic human disease.[1] Influenza A viruses are further categorized into subtypes based on two surface antigens: hemagglutinin (H) and neuraminidase (N). Influenza B viruses are not categorized into subtypes. Both influenza A and B viruses are further separated into groups based on antigenic characteristics. New influenza virus variants result from frequent antigenic change (ie, antigenic drift), resulting from point mutations that occur during viral replication. Influenza B viruses undergo antigenic drift less rapidly than influenza A viruses. Since 1977, influenza A (H1N1) viruses, influenza A (H3N2) viruses, and influenza B viruses have been in global circulation. In 2001, influenza A (H1N2) viruses that probably emerged after genetic reassortment between human A (H3N2) and A (H1N1) viruses began circulating widely.

A person's immunity to the surface antigens, especially hemagglutinin, reduces the likelihood of infection and severity of disease if infection occurs. Antibody against one influenza virus type or subtype confers little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual incorporation of one or more new strains in each year's influenza vaccine.[1]

Formal subclassification utilizing neuraminidase antigens has not been done for influenza B viruses.

The incubation period for influenza is 1–4 days with an average of 2 days. Adults typically are infectious from the day before symptoms begin through approximately 5 days after illness onset. Children can be infectious for ≥10 days, and young children can shed virus for ≤6 days before their illness onset. Severely immunocompromised persons can shed virus for weeks or months.

Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (eg, fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis). Among children, otitis media, nausea and vomiting are also commonly reported with influenza illness.

Influenza illness typically resolves after a limited number of days for the majority of persons, although cough and malaise can persist for >2 weeks. Among certain persons, influenza can exacerbate underlying medical conditions (eg, pulmonary or cardiac disease), lead to secondary bacterial pneumonia or primary influenza viral pneumonia, or occur as part of a coinfection with other viral or bacterial pathogens. Young children with influenza infection can have initial symptoms mimicking bacterial sepsis with high fevers and ≤20% of children hospitalized with influenza can have febrile seizures. Influenza infection has also been associated with encephalopathy, transverse myelitis, Reye syndrome, myositis, myocarditis, and pericarditis.[1]

The risks for complications, hospitalizations, and deaths from influenza are higher among persons aged ≥65 years, young children, and persons of any age with certain underlying health conditions than among healthy older children and younger adults.[1]

Among children aged 0–4 years, hospitalization rates have ranged from approximately 500/100,000 children for those with high-risk medical conditions to 100/100,000 children for those without high-risk medical conditions, and are comparable to rates reported among persons aged ≥65 years.[1] In addition, influenza is a leading cause of death in young children and, along with pneumonia, is the sixth leading cause of death in those 1–4 years of age.[2]

During influenza epidemics from 1969–1970 through 1994–1995, the estimated overall number, for all ages, of influenza-associated hospitalizations in the US has ranged from approximately 16,000 to 220,000/epidemic. An average of approximately 114,000 influenza-related excess hospitalizations occurred per year, with 57% of all hospitalizations occurring among persons aged <65 years. Since the 1968 influenza A (H3N2) virus pandemic, the greatest numbers of influenza-associated hospitalizations have occurred during epidemics caused by type A (H3N2) viruses, with an estimated average of 142,000 influenza-associated hospitalizations per year.[1]

Influenza-related deaths can result from pneumonia as well as from exacerbations of cardiopulmonary conditions and other chronic diseases. Older adults account for ≥90% of deaths attributed to pneumonia and influenza. In a recent study of influenza epidemics, approximately 19,000 influenza-associated pulmonary and circulatory deaths per influenza season occurred during 1976–1990, compared with approximately 36,000 deaths per influenza season during 1990–1999. Estimated rates of influenza-associated pulmonary and circulatory deaths per 100,000 persons were 0.4–0.6 among persons aged 0–49 years, 7.5 among persons aged 50–64 years, and 98.3 among persons aged ≥65 years.[1] In the US, the number of influenza-associated deaths might be increasing in part because the number of older persons is increasing.[1,4] In addition, influenza seasons in which influenza A (H3N2) viruses predominate are associated with higher mortality; influenza A (H3N2) viruses predominated in 90% of influenza seasons from 1990–1999 compared with 57% of influenza seasons from 1976–1990.[1]

Vaccinating persons at high risk for complications and their contacts each year before seasonal increases in influenza virus circulation is the most effective means of reducing the effect of influenza. Vaccination coverage can be increased by administering vaccine to persons during hospitalizations or routine health-care visits before the influenza season, making special visits to physicians' offices or clinics unnecessary. Vaccination of health-care workers and other persons in close contact with persons at increased risk for severe influenza illness can also reduce transmission of influenza and subsequent influenza-related complications.[1]

Inactivated influenza vaccines are standardized to contain the hemagglutinins of strains (ie, typically two type A and one type B), representing the influenza viruses likely to circulate in the US in the upcoming winter. The effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation. The majority of vaccinated children and young adults develop high postvaccination hemagglutination-inhibition antibody titers. These antibody titers are protective against illness caused by strains similar to those in the vaccine.[1]

When the vaccine and circulating viruses are antigenically similar, influenza vaccine prevents illness in approximately 70%–90% of healthy adults aged <65 years. Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health-care resources, including the use of antibiotics, when the vaccine and circulating viruses are well-matched.[1]

Children aged as young as 6 months develop protective levels of antibody after influenza vaccination, although the antibody response among children at high risk for influenza-related complications might be lower than among healthy children.[1] (See PEDIATRIC USE subsection.)

Older persons aged ≥65 years and persons with certain chronic diseases might develop lower postvaccination antibody titers than healthy young adults and thus can remain susceptible to influenza-related upper respiratory tract infection. However, among such persons, the vaccine can be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death among adults aged ≥65 years with and without high risk medical conditions (eg, heart disease and diabetes). Among elderly persons living outside of nursing homes or similar chronic-care facilities, influenza vaccine is 30%–70% effective in preventing hospitalization for pneumonia and influenza. Among elderly persons residing in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications, and deaths. Among this population, the vaccine can be 50%–60% effective in preventing hospitalization or pneumonia and 80% effective in preventing death, although the effectiveness in preventing influenza illness often ranges from 30%–40%.[1]

INDICATIONS AND USAGE

Fluzone vaccine is indicated for active immunization against influenza disease caused by influenza virus types A and B contained in the vaccine in subjects from 6 months of age and older.

The optimal time to vaccinate is usually during October–November. ACIP recommends that vaccine providers focus their vaccination efforts in October and earlier primarily on persons aged ≥50 years, persons aged <50 years at increased risk for influenza-related complications (including children aged 6–23 months), household contacts of persons at high risk (including out-of-home caregivers and household contacts of children aged 0–23 months), and health-care workers. Vaccination of children aged <9 years who are receiving vaccine for the first time should also begin in October or earlier because those persons need a booster dose 1 month after the initial dose. Efforts to vaccinate other persons who wish to decrease their risk for influenza infection should begin in November; however, if such persons request vaccination in October, vaccination should not be deferred.[1] After November, many persons who should or want to receive influenza vaccine remain unvaccinated. In addition, substantial amounts of vaccine remained unused during the past four influenza seasons. To improve vaccine coverage, influenza vaccine should continue to be offered in December and throughout the influenza season as long as vaccine supplies are available, even after influenza activity has been documented in the community. In the US, seasonal influenza activity can begin to increase as early as October or November, but influenza activity has not reached peak levels in the majority of recent seasons until late December–early March. Therefore, although the timing of influenza activity can vary by region, vaccine administered after November is likely to be beneficial in the majority of influenza seasons. Adults develop peak antibody protection against influenza infection 2 weeks after vaccination.[1]

To avoid missed opportunities for vaccination of persons at high risk for serious complications, such persons should be offered vaccine beginning in September during routine health-care visits or during hospitalizations, if vaccine is available. In facilities housing older persons (eg, nursing homes), vaccination before October typically should be avoided because antibody levels in such persons can begin to decline within a limited time after vaccination.

Persons planning substantial organized vaccination campaigns should consider scheduling these events after mid-October because the availability of vaccine in any location cannot be ensured consistently in the early fall. Scheduling campaigns after mid-October will minimize the need for cancellations because vaccine is unavailable.[1] (For information on vaccination of travelers, see TRAVELERS subsection.)

Dosage recommendations vary according to age group (**TABLE 3**). Among previously unvaccinated children aged <9 years, who are receiving influenza vaccine for the first time, two doses administered ≥1 month apart are recommended for satisfactory antibody responses. If possible, the second dose should be administered before December. If a child aged <9 years receiving vaccine for the first time does not receive a second dose of vaccine within the same season, only 1 dose of vaccine should be administered the following season (see **TABLE 3**). Among adults, studies have indicated limited or no improvement in antibody response when a second dose is administered during the same season. Even when the current influenza vaccine contains ≥1 antigen administered in previous years, annual vaccination with the current vaccine is necessary because immunity declines during the year after vaccination. Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season.[1]

The intramuscular route is recommended for influenza vaccine (see **DOSAGE AND ADMINISTRATION** section). Dosage recommendations for the 2006–2007 season are given in Table 3. Guidelines for the use of vaccine among certain patient populations are given below.[1]

Influenza vaccine (subvirion) is strongly recommended for any person aged ≥6 months who is at increased risk for complications of influenza. In addition, health-care workers and other persons (including household members) in close contact with persons at high risk should be vaccinated to decrease the risk of transmitting influenza to persons at high risk. Influenza vaccine also can be administered to any person aged ≥6 months to reduce the chance of becoming infected with influenza.[1] (See TARGET GROUPS FOR VACCINATION subsection.)

SAFETY AND EFFECTIVENESS OF FLUZONE VACCINE (SUBVIRION) IN INFANTS BELOW THE AGE OF 6 MONTHS HAVE NOT BEEN ESTABLISHED.

TARGET GROUPS FOR VACCINATION

Persons at Increased Risk for Complications

According to ACIP, vaccination is recommended for the following groups of persons who are at increased risk for complications from influenza:[1]

- persons aged ≥65 years;
- residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;

- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma;
- adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV]);
- children and adolescents (aged 6 months–18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for developing Reye syndrome after influenza infection;
- women who will be pregnant during the influenza season; and
- children aged 6–23 months.

In 2000, approximately 73 million persons in the US were included in one or more of these target groups, including 35 million persons aged ≥65 years; and 12 million adults aged 50–64 years, 18 million adults aged 18–49 years, and 8 million children aged 6 months–17 years with one or more medical conditions that are associated with an increased risk of influenza-related complications.[1]

Persons Aged 50 to 64 Years

Vaccination is recommended for persons aged 50–64 years because this group has an increased prevalence of persons with high risk conditions. In 2000, approximately 42 million persons in the US were aged 50–64 years, of whom 12 million (29%) had one or more high-risk medical conditions. Influenza vaccine has been recommended for this entire age group to increase the low vaccination rates among persons in this age group with high-risk conditions. Age-based strategies are more successful in increased vaccine coverage than patient-selection strategies based on medical conditions. Persons aged 50–64 years without high-risk conditions also receive benefit from vaccination in the form of decreased rates of influenza illness, decreased work absenteeism, and decreased need for medical visits and medication, including antibiotics. Further, 50 years is an age when other preventive services begin and when routine assessment of vaccination and other preventive services has been recommended.[1]

Also, persons who smoke tobacco products are at increased risk for influenza-related complications and therefore should receive influenza vaccine.[5-7]

Persons Who Can Transmit Influenza to Those at High Risk:[1]

Persons who are clinically or subclinically infected can transmit influenza virus to persons at high risk for complications from influenza. Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might reduce influenza-related deaths among persons at high risk. Evidence from two studies indicates that vaccination of health-care personnel is associated with decreased deaths among nursing home patients. Vaccination of health-care personnel and others in close contact with persons at high risk, including household contacts, is recommended. The following groups should be vaccinated:[1]

- physicians, nurses, and other personnel in both hospital and outpatient-care settings, including medical emergency response workers (eg, paramedics and emergency medical technicians);
- employees of nursing homes and chronic-care facilities who have contact with patients or residents;
- employees of assisted living and other residences for persons in groups at high risk;
- persons who provide home care to persons in groups at high risk; and
- household contacts (including children) of persons in groups at high risk.

In addition, because children aged 0–23 months are at increased risk for influenza-related hospitalization, vaccination is recommended for their household contacts and out-of-home caretakers, particularly for contacts of children aged 0–5 months, because influenza vaccines have not been approved by the US Food and Drug Administration (FDA) for use among children aged <6 months.[1]

General Population

Physicians should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza (the vaccine can be administered to children aged ≥6 months) depending on vaccine availability. Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students or other persons in institutional settings (eg, those who reside in dormitories) should be encouraged to receive vaccine to minimize the disruption of routine activities during epidemics.[1]

Healthy Young Children

Studies indicate that rates of hospitalization are higher among young children than older children when influenza viruses are in circulation. The increased rates of hospitalization are comparable with rates for other groups considered at high risk for influenza-related complications. However, the interpretation of these findings has been confounded by co-circulation of respiratory syncytial viruses, which are a cause of serious respiratory viral illness among children and which frequently circulate during the same time as influenza viruses. Two recent studies have attempted to separate the effects of respiratory syncytial viruses and influenza viruses on rates of hospitalization among children who do not have high-risk conditions. Both studies reported that otherwise healthy children aged <2 years, and possibly children aged 2–4 years, are at increased risk for influenza-related hospitalization compared with older healthy children. Some studies report that trivalent inactivated influenza vaccine decreases the incidence of influenza-associated otitis media among young children by approximately 30%.[1]

Because children aged 6–23 months are at substantially increased risk for influenza-related hospitalizations, ACIP, the American Academy of Pediatrics, and the American Academy of Family Physicians recommends vaccination of all children in this age group. ACIP continues to recommend influenza vaccination of persons aged ≥6 months who have high-risk medical conditions.[1]

Pregnant Women

Because of the increased risk for influenza-related complications, ACIP recommends that women who will be pregnant during the influenza season should be vaccinated. One study of influenza vaccination of >2,000 pregnant women demonstrated no adverse fetal effects associated with influenza vaccine.[1] (Refer to PREGNANCY CATEGORY C statement.)

The majority of influenza vaccine distributed in the US contains the preservative thimerosal, a mercury-containing compound, but influenza vaccine with a reduced or no thimerosal content is available. Thimerosal has been used in US vaccines since the 1930s. No data or evidence exists of any harm caused by the level of mercury exposure that might occur from influenza vaccination. Because pregnant women are at increased risk for influenza-related complications and because a substantial safety margin has been incorporated into the health guidance values for organic mercury exposure, the benefit of influenza vaccine with standard thimerosal content outweighs the potential risk, if any, for thimerosal.

Breastfeeding Mothers

Influenza vaccine does not adversely affect mothers or their infants who are being breastfed. Breastfeeding does not adversely affect the immune response and is not a contraindication for vaccination.[1]

Persons Infected with Human Immunodeficiency Virus (HIV)

Limited information is available regarding the frequency and severity of influenza illness or the benefits of influenza vaccination among persons with HIV infection. However, a retrospective study of young and middle-aged women found that the attributable risk for cardiopulmonary hospitalizations among women with HIV infection was higher during influenza seasons than in the peri-influenza periods. The risk for hospitalization was higher for HIV-infected women than for women with other well-recognized high-risk conditions, including chronic heart and lung diseases. Other reports indicate that influenza symptoms might be prolonged and the risk for complications from influenza increased for certain HIV-infected persons.[1]

Influenza vaccination has been demonstrated to produce substantial antibody titers against influenza among vaccinated HIV-infected persons who have minimal acquired immunodeficiency syndrome-related symptoms and high $CD4^+$ T-lymphocyte cell counts. A limited, randomized, placebo-controlled trial determined that influenza vaccine was highly effective in preventing symptomatic, laboratory-confirmed influenza infection among HIV-infected persons with a mean of 400 $CD4^+$ T-lymphocyte cells/mm^3; a limited number of persons with $CD4^+$ T-lymphocyte cell counts of <200 were included in that study. Among persons who have advanced HIV disease and low $CD4^+$ T-lymphocyte cell counts, influenza vaccine might not induce protective antibody titers; a second dose of vaccine does not improve the immune response in these persons.[1]

One study determined that HIV RNA (ribonucleic acid) levels increased transiently in one HIV-infected patient after influenza infection. Studies have demonstrated a transient (ie, 2–4-week) increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration. Other studies using similar laboratory techniques have not documented a substantial increase in replication of HIV. Deterioration of $CD4^+$ T-lymphocyte cell counts or progression of HIV disease have not been demonstrated among HIV-infected persons after influenza vaccination compared with unvaccinated persons. Limited information is available concerning the effect of antiretroviral therapy on increases in HIV RNA levels after either natural influenza infection or influenza vaccination. Because influenza can result in serious illness, and because influenza vaccination can result in the production of protective antibody titers, vaccination will benefit HIV-infected patients, including HIV-infected pregnant women.[1]

Travelers

The risk of exposure to influenza during travel depends on the time of year and destination. In the tropics, influenza can occur throughout the year. In the temperate regions of the Southern Hemisphere, the majority of influenza activity occurs during April–September. In temperate climate zones of the Northern and Southern Hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling as part of large organized tourist groups (eg, on cruise ships) that include persons from areas of the world where influenza viruses are circulating. Persons at high risk for complications of influenza who were not vaccinated with influenza vaccine during the preceding fall or winter should consider receiving influenza vaccine before travel if they plan to:[1]

- travel to the tropics;
- travel with organized tourist groups at any time of year; or
- travel to the Southern Hemisphere during April–September.

No information is available regarding the benefits of revaccinating persons before summer travel who were already vaccinated in the preceding fall. Persons at high risk who received the previous season's vaccine before travel should be revaccinated with the current vaccine in the following fall or winter. Persons aged ≥50 years and others at high risk might want to consult with their physicians before embarking on travel during the summer to discuss the symptoms and risks for influenza and the advisability of carrying antiviral medications for either prophylaxis or treatment of influenza.[1]

CONCOMITANT ADMINISTRATION WITH OTHER VACCINES

CONCURRENT USE WITH PNEUMOCOCCAL VACCINE. Influenza vaccine has been shown in clinical studies to be acceptable for concurrent use with pneumococcal vaccine using separate syringes at different sites.[8] Although Influenza Virus Vaccine is recommended for annual use, the pneumococcal vaccine is not.[9,10,11] When indicated, pneumococcal vaccine should be administered to patients who are uncertain regarding their vaccination history. No studies regarding the concomitant administration of inactivated influenza vaccine and other childhood vaccines have been conducted. Children at high risk for influenza-related complications, including those aged 6–23 months, can receive influenza vaccine at the same time they receive other routine vaccinations.[11]

CONTRAINDICATIONS

Fluzone vaccine should not be administered to anyone with known systemic hypersensitivity reactions to egg proteins (eggs or egg products), to chicken proteins, or any component of Fluzone vaccine or a life-threatening reaction after previous administration of the vaccine or a vaccine containing the same substances. (Refer to **DESCRIPTION** and **WARNINGS** sections.)

Vaccination may be postponed in case of febrile or acute disease.

Immunization should be delayed in a patient with an active neurologic disorder, but should be considered when the disease process has been stabilized.

WARNINGS

Fluzone should not be administered to individuals who have a prior history of Guillain-Barré syndrome (GBS) (see **ADVERSE REACTIONS** section).

If Fluzone vaccine is used in persons deficient in producing antibodies, whether due to genetic defect, immunodeficiency disease, or immunosuppressive therapy, the expected antibody response may not be obtained.

As with any vaccine, vaccination with Fluzone vaccine may not protect 100% of individuals.

PRECAUTIONS

GENERAL

Care is to be taken by the health-care provider for the safe and effective use of this vaccine.

Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.

Because intramuscular injection can cause injection site hematoma, Fluzone vaccine should not be given to persons with any bleeding disorder, such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefits clearly outweigh the risk of administration. If the decision is made to administer Fluzone vaccine in such persons, it should be given with caution, with steps taken to avoid the risk of hematoma formation following injection.

As with all injectable vaccines, appropriate medical treatment and supervision should be readily available for immediate use in case of a rare anaphylactic reaction following the administration of the vaccine.

As a precautionary measure, epinephrine injection (1:1000) must be immediately available in case of unexpected anaphylactic or serious allergic reactions.

Influenza virus is remarkable in that minor antigenic changes occur frequently (antigenic drift), whereas a significant antigenic change leading to a pandemic strain (antigenic shift) is unpredictable. *It is known that Influenza Virus Vaccine, as now constituted, is not effective against all possible strains of influenza virus. Protection is limited to those strains of virus from which the vaccine is prepared or to closely related strains.*

During the course of any febrile respiratory illness or other active infection, use of Influenza Virus Vaccine should be delayed.

Since the likelihood of febrile convulsions is greater in children aged 6 months–35 months, special care should be taken in weighing relative risks and benefits of vaccination.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity to the vaccine or similar vaccine, previous immunization history, current health status (see **CONTRAINDICATIONS** and **WARNINGS** sections) and a knowledge of the current literature concerning the use of the vaccine under consideration.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be disposed of according to biohazard waste guidelines.

INFORMATION FOR PATIENT

Patients, parents or guardians should be fully informed by their health-care provider of the benefits and risks of immunization with Influenza Virus Vaccine.

Patients, parents or guardians should be instructed to report any serious adverse reactions to their health-care provider.

DRUG INTERACTION

Although influenza vaccination can inhibit the clearance of warfarin, theophylline, phenytoin, and aminopyrine therapy, studies have failed to show any adverse clinical effects attributable to these drugs in patients receiving influenza vaccine.[12-18]

If Fluzone vaccine is administered to immunosuppressed persons or persons receiving immunosuppressive therapy, the expected antibody response may not be obtained. This includes patients with asymptomatic HIV infection, AIDS or AIDS-Related Complex, severe combined immunodeficiency, hypogammaglobulinemia, or aggammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation.[19]

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with Influenza Virus Vaccine. It is not known whether Influenza Virus Vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Influenza Virus Vaccine should be given to a pregnant woman only if clearly needed. For guidance regarding use in pregnant women, see **INDICATIONS AND USAGE** section.

PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF FLUZONE VACCINE (SUBVIRION) IN INFANTS BELOW THE AGE OF 6 MONTHS HAVE NOT BEEN ESTABLISHED.

ACIP recommends that healthy children aged 6–23 months, and close contacts of children aged 0–23 months, be vaccinated against influenza (see TARGET GROUPS FOR VACCINATION subsection).[1]

Data in children as young as 6 months show that protective levels of antibody (hemagglutination inhibition antibody titers ≥1:40) can be attained after influenza vaccination, although the antibody responses among children at high risk of influenza-related complications might be lower than among healthy children.[1]

In a randomized study among children aged 1–15 years, inactivated influenza vaccine was 77%–91% effective against influenza respiratory illness and was 44%–49%, 74%–76%, and 70%–81% effective against influenza seroconversion among children aged 1–5, 6–10, and 11–15 years respectively.[1]

In a randomized, double-blind, placebo-controlled study of the efficacy of Fluzone vaccine against culture positive influenza in healthy children aged 6–24 months was conducted over two seasons.

During the 1999–2000 influenza season, the efficacy of the vaccine against culture-proven influenza in the first cohort was 66% (95% CI 34%–82%). In this year, culture-proven influenza was identified in 15 (5.5%) of 273 children in the vaccine group and 22 (15.9%) of 138 children in the placebo group. During the 2000–2001 season, the efficacy in the second cohort was -7% (95% CI -247% to 67%), however the overall attack rate was 3%, a rate that inhibited obtaining true efficacy.[20] In a study using 2 doses of Fluzone vaccine in healthy children aged 6–24 months, the following immunogenicity results were obtained over two consecutive seasons in two different cohorts:[20]

TABLE 1[20]

GEOMETRIC MEAN TITER (GMT) AND PERCENTAGE (%) SEROPROTECTED (TITER 1:40 OR GREATER) (N = 31–35)

ANTIGEN	PRE-VACCINE GMT (% TITER ≥40)	POST DOSE 2 GMT (% TITER ≥40)
A (H3N2)		
Cohort 1 (N = 35)	18.5 (11.4)	68.3 (88.6)
Cohort 2 (N = 31)	9.5 (22.6)	69.2 (96.8)
A (H1N1)		
Cohort 1 (N = 35)	5.0 (0)	46.8 (91.4)
Cohort 2 (N = 31)	5.0 (0)	44.3 (90.3)
B		
Cohort 1 (N = 35)	9.8 (17.1)	130.0 (91.4)
Cohort 2 (N = 31)	5.0 (0)	42.8 (90.3)

N = Number of children

An analysis of 215,600 children aged <18 years and 8,476 children aged 6–23 months enrolled in 1 of 5 health maintenance organizations reported no increase in biologically plausible medically attended events during the 2 weeks after inactivated influenza immunization.[1] Between January 1, 1991–January 23, 2003, Vaccine Adverse Events Reporting System (VAERS) received 1,072 reports of adverse events among children <18 years, including 174 reports of adverse events among children aged 6–23 months. The number of doses given to children during this time period is unknown. The most frequently reported events among children were fever, injection-site reaction, and rash. (See **CLINICAL PHARMACOLOGY** and **INDICATIONS AND USAGE** sections.)

GERIATRIC USE

In a systematic review of adverse events by Sanofi Pasteur Inc. for two previous influenza seasons, there were no differences in reports of adverse events occurring with any distributed lots of Fluzone vaccine for 1999–2001. In addition, there were no observed changes in the number or types of adverse events reported for Fluzone vaccine during 1999–2001 for persons 65 years and older.[21]

There are age-related differences in immune responses to many vaccines. The differences have been reviewed for travel vaccines.[22] Lower immunogenicity for influenza vaccines given to elderly persons compared to young adults has also been observed.[21]

In a study of the immunogenicity of Fluzone vaccine in a geriatric population,[21] the following results were obtained using Fluzone vaccine for 1999–2000:

TABLE 2[21]

GEOMETRIC MEAN TITER (GMT) AND PERCENTAGE (%) SEROPROTECTED (TITER 1:40 OR GREATER) (N = 58–62)

ANTIGEN	PRE-VACCINE GMT	POST GMT (% TITER ≥40)
A (H3N2)		
Cohort 1999		
Young (N = 60)	16.6	53.1 (72)
Elderly (N = 61)	20.1	58.2 (70)
Cohort 2000		
Young (N = 58)	18.6	72.7 (79)
Elderly (N = 62)	18.1	49.7 (68)
A (H1N1)		
Cohort 1999		
Young (N = 60)	11.1	35.6 (49)
Elderly (N = 61)	12.2	26.5 (38)
Cohort 2000		
Young (N = 58)	8.9	35.9 (54)
Elderly (N = 62)	6.7	16.0 (23)
B		
Cohort 1999		
Young (N = 60)	14.4	41.4 (38)
Elderly (N = 61)	9.9	19.4 (10)
Cohort 2000		
Young (N = 58)	9.4	21.5 (38)
Elderly (N = 62)	7.4	9.9 (11)

N = Number of participants

A randomized trial among noninstitutionalized persons aged ≥60 years reported a vaccine efficacy of 58% against influenza respiratory illness, but indicated that efficacy might be lower among those aged ≥70 years. The vaccine can also be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death among adults ≥65 years with and without high-risk medical conditions (eg, heart disease and diabetes). Among elderly persons living outside of nursing homes or similar chronic-care facilities, influenza vaccine is 30%–70% effective in preventing hospitalization for pneumonia and influenza.[1] (See **CLINICAL PHARMACOLOGY** section.)

ADVERSE REACTIONS

When educating patients regarding potential side effects, clinicians should emphasize that 1) inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza; and 2) coincidental respiratory disease unrelated to influenza vaccine can occur after vaccination.[1]

LOCAL REACTIONS

In placebo-controlled studies among adults, the most frequent side effect of vaccination is soreness at the vaccination site (affecting 10%–64% of patients) that lasts <2 days, local pain and swelling. These local reactions typically are mild and rarely interfere with the person's ability to conduct usual daily activities.[1]

SYSTEMIC REACTIONS

Fever, malaise, myalgia, and other systemic symptoms can occur following vaccination and most often affect persons who have had no prior exposure to the influenza virus antigens in the vaccine (eg, young children).[1,23] These reactions begin 6–12 hours after vaccination and can persist for 1–2 days. Recent placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of split-virus influenza vaccine is not associated with higher rates of systemic symptoms (eg, fever, malaise, myalgia, and headache) when compared with placebo injections.[1]

Immediate – presumably allergic – reactions (eg, hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. These reactions probably result from hypersensitivity to certain vaccine components; the majority of reactions probably are caused by residual egg protein. Although current influenza vaccines contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Persons who have had hives or swelling of the lips or tongue or have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who have documented immunoglobulin E (IgE)–mediated hypersensitivity to eggs, including those who have had occupational asthma or other allergic responses to egg protein, also might be at increased risk for allergic reactions to influenza vaccine, and consultation with a physician should be considered. Protocols have been published for safely administering influenza vaccine to persons with egg allergies.[1,24]

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS).[1,25] Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear.[1] Obtaining strong epidemiologic evidence for such a possible limited increase in risk is difficult for such a rare condition as GBS, which has an annual incidence of 10–20 cases/1 million adults,[1] and stretches the limits of epidemiologic investigation.

During three of four influenza seasons studied from 1977–1991, the overall relative risk estimates for GBS after influenza vaccination were slightly elevated but were not statistically significant in any of these studies. However, in a study of the 1992–1993 and 1993–1994 seasons, the overall relative risk for GBS was 1.7 (95% confidence interval = 1.0–2.8; p = 0.04) during the 6 weeks after vaccination, representing approximately 1 additional case of GBS/1 million persons vaccinated. The combined number of GBS cases peaked two weeks after vaccination. Thus, investigations to date indicate that there is no substantial increase in GBS associated with influenza vaccines (other than the swine influenza vaccine in 1976), and that, if influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.[1]

Even if GBS were a true side effect of vaccination in the years after 1976, the estimated risk for GBS of approximately 1 additional case/1,000,000 persons vaccinated is substantially less than the risk for severe influenza, which could be prevented by vaccination among all age groups, especially persons aged ≥65 years and those who have medical indications for influenza vaccination.[1]

The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death substantially outweigh the possible risks for developing vaccine-associated GBS. The average case-fatality ratio for GBS is 6% and increases with age. No evidence indicates that the case-fatality ratio for GBS differs among vaccinated persons and those not vaccinated.[1]

The incidence of GBS among the general population is low, but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history. Thus, the likelihood of coincidently experiencing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of GBS is unknown.[1]

Neurological disorders temporally associated with influenza vaccination such as encephalopathy, optic neuritis/neuropathy,[26,27] partial facial paralysis, and brachial plexus neuropathy have been reported. However, no cause and effect has been established.[21,28] Almost all persons affected were adults, and the described clinical reactions began as soon as a few hours and as late as 2 weeks after vaccination. Full recovery was almost always reported.[25,29,30]

Microscopic polyangitis (vasculitis) has been reported temporally associated with influenza vaccination.[31]

REPORTING OF ADVERSE EVENTS

Reporting by patients, parents, or guardians of all adverse events after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.[32]

The health-care providers also should report these events to the Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration whenever solution and container permit. If either of these conditions exist, the vaccine should not be administered.

To help avoid HIV (AIDS), HBV (Hepatitis) and other infectious diseases due to accidental needlesticks, contaminated needles should not be recapped or removed, unless there is no alternative or such action is required by a specific medical procedure.

The vial should be shaken well before withdrawing each dose.

The prefilled syringe should be shaken well before administering each dose. The 0.25 mL prefilled syringe is preferred for use when 0.25 mL is indicated for children.

Do NOT inject intravenously.

Injections of Influenza Virus Vaccine should be administered intramuscularly, preferably in the region of the deltoid muscle, in adults and older children. A needle length of ≥1 inch is preferred for these age groups because needles <1 inch might be of insufficient length to penetrate muscle tissue in certain adults and older children. Before injection, the skin over the site to be injected should be cleansed with a suitable germicide.

Infants and young children should be vaccinated in the anterolateral aspect of the thigh. ACIP recommends a needle length of 7/8–1 inch for children <12 months for intramuscular vaccination into the anterolateral thigh. When injecting into the deltoid muscle among children with adequate deltoid muscle mass, a needle length of 7/8–1-1/4 inches is recommended.[1]

Influenza vaccine should be offered beginning in September (see **INDICATIONS AND USAGE** section).

Children <9 years who have not previously been vaccinated should receive two doses of vaccine ≥1 month apart to maximize the likelihood of a satisfactory antibody response to all three vaccine antigens. If possible, the second dose should be administered before December.[1]

Fluzone vaccine (Subvirion) is to be used for persons 6 months of age and older. Fluzone vaccine (Subvirion) is NOT approved for infants under 6 months of age. The dosage is as follows:

TABLE 3[1] **INFLUENZA VACCINE DOSAGE BY AGE GROUP 2006–2007 SEASON**

Age Group	Dosage	No. of Doses	Route§
6–35 months	0.25 mL	1 or 2*	Intramuscular
3–8 years	0.50 mL	1 or 2*	Intramuscular
≥9 years	0.50 mL	1	Intramuscular

§ For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.

* Two doses administered at least one month apart are recommended for children <9 years who are receiving influenza vaccine for the first time.

HOW SUPPLIED

Syringe, without needle, 0.25 mL (contains NO preservative) (10 per package). Shake syringe well before administering. Product No. 49281-006-25 – CPT® Code: 90655, age 6–35 months.

Syringe, without needle, 0.5 mL (contains NO preservative) (10 per package). Shake syringe well before administering. Product No. 49281-006-50 – CPT® Code: 90656, age 36 months and older.

Vial, 0.5 mL (contains NO preservative) (10 per package). Shake vial well before administering. Product No. 49281-006-10 – CPT® Code: 90656, age 36 months and older.

Vial, 5 mL (contains preservative) for administration with needle and syringe or sterile disposable unit. Shake vial well before withdrawing each dose. Product No. 49281-378-15 – CPT® Code: 90658, 0.5 mL, age 36 months and older; CPT® Code: 90657, 0.25 mL, age 6–35 months.

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STORAGE

Store at 2° to 8°C (35° to 46°F). **DO NOT FREEZE.**

REFERENCES

1. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2004;53:1-40. **2.** Anderson, RN, et al. National Vital Statistics Reports 2003;Vol 25(9). **3.** Thompson, WW, et al. JAMA 2003;Vol 289(2):179-186. **4.** Nichol KL, et al. N Engl J Med 2003;348:1322-1332. **5.** Mulloy E. Ir Med J 1996;Vol 89(6):202,204. **6.** Zimmerman RK, et al. Am Fam Physician 1995;51(4):859-867. **7.** Rothbarth PH, et al. Am J Respir Crit Care Med 1995;151:1682-1686. **8.** Honkanen P, et al. Arch Intern Med 1996;156:205-208. **9.** Grilli G, et al. Eur J Epidemiol 1997;13:287-291. **10.** DeStefano F, et al. JAMA 1982;247:2551-2554. **11.** CDC. MMWR 2003;52:1-33. **12.** Renton KW, et al. Can Med Assoc J 1980;123:288-290. **13.** Fischer RG, et al. Can Med Assoc J 1982;126: 1312-1313. **14.** Lipsky BA, et al. Ann Intern Med 1984;100:6:835-837. **15.** Kramer P, et al. Clin Pharmacol Ther 1984;Vol 35,#3: 416-418. **16.** Patriarca PA, et al. N Engl J Med 1983;308:1601-1602. **17.** Levine M, et al. Clin Pharm 1984;3:505-509. **18.** Kilbourne ED. Vaccines (Plotkin and Mortimer eds.) Saunders Company 1988;429. **19.** ACIP. MMWR 1986;35:595-606. **20.** Hoberman A, et al. JAMA 2003;290(12):1608-1616. **21.** Data on File, Sanofi Pasteur Inc. 1994: MKT5720. **22.** Leder K, et al. Clin Infect Dis 2001;33:1553-1566. **23.** Barry DW, et al. Am J Epidemiol 1976;104:47-59. **24.** Murphy KR, et al. J Pediatr 1985;106: 931-933. **25.** Schonberger LB, et al. Am J Epidemiol 1979;110:105-123. **26.** Hull TP, et al. Am J Opthalmol 1997;703-704. **27.** Kawasaki A, et al. J Neuro-Opthalmol 1998;18(1):56-59. **28.** CDC. Surveillance Report No. 3, 1985-1986, Issued February 1989. **29.** Retaillaiu HF, et al. Am J Epid III 1980;(3): 270-278. **30.** Guerrero IC, et al. N Engl J Med 1979;300(10):565. **31.** Kelsall JT, et al. J Rheumatol 1997;1198-1202. **32.** CDC. MMWR 1990;39:730-733.

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Product information
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